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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,233	10/24/2003	Zehra Kaymakcalan	117813-99302	1420

87501 7590 04/08/2011

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
04/08/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,233	KAYMAKCALAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,21,22,24,31,34,35,42,43,45,48 and 60-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,21,22,24,31,34,35,42,43,45,48 and 60-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-16-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed February 7, 2011 are acknowledged.

   Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 are under examination wherein the elected species of disorder to be treated is rheumatoid arthritis.

   The previous rejection under 35 U.S.C. § 102(b) or in the alternative 103(a) in view of Le have been withdrawn in view of applicant's arguments.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 stand rejected, and new claims 60-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010.

   Applicant is in possession of the method of claim 15 if it is limited to "a low dose of 0.1-0.21 mg/kg at a frequency of once per week" or the methods of claims 21 and 42 if they are limited to "a low dose of 0.06-0.21 mg/kg at a frequency of once per week", however applicant is not in possession of the breadth of currently claimed methods of treatment.

   Applicant argues the claims as amended satisfy the written description requirement because they believe "the currently recited ranges are adequately represented by the disclosed species, such as 0.1 mg/kg, especially in view of the data of 0.01 mg/kg and 0.5 mg/kg. See, for example, Figures 1, 4, and 5."

   In support of this proposition applicant points to the date of Figures 5A-D and alleges the efficacy of 0.1 mg/kg/week and 0.5 mg/kg/week D2E7 are similar: "For instance, in Figure 5A…0.1 mg/kg clearly gives rise to the same (if not better) efficacy than 0.5 mg/kg. The same result is obtained for "cartilage erosion" in Figure 5B (note that the 0.1 mg/kg and 0.5 mg/kg bars are both approaching zero)…"

   Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010.

   While the examiner does not agree with applicant's data analysis as it pertains to Figure 5A – 0.5 mg/kg D2E7 seems to be totally suppressive while 0.1 mg/kg is only partially suppressive

– or Figure 5B - why does applicant say D2E7 treatment is "approaching zero" when the examiner would interpret the graphic as saying that there was no detected cartilage erosion for both 0.1 and 0.5 D2e7 (and the examiner would appreciate clarification from applicant as to what is the correct interpretation of the data in these figures) – the examiner does agree that given the trends in the data for Figure 5 applicant has established possession of the methods of claims 21 and 42 if they were limited to "a low dose of 0.06-0.21 mg/kg at a frequency of once per week".

However, applicant is not in possession of the method of treatment where a low dose of about 0.06-0.21 mg/kg at a frequency of about once per week, such that at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity is alleviated, as demonstrable after 10 treatments. Applicant's argument hinges on the data trends seen after administering 10 **weekly** doses of 0.1 mg/kg or 0.5 mg/kg of D2E7 starting from the mouse's first week of life and yet the instant claims encompass in their breadth **less than weekly** dosing **and** dosage at below 0.1 mg/kg.

Given this claim breadth and the lack of any working examples in **less than weekly** dosing **and** dosage below 0.1 mg/kg the skilled artisan would not recognize applicant to be in possession of the claimed invention.

Moreover, given that the sole working example of the instant specification is an experiment performed with Tg197 mice that were treated both prophylactically and therapeutically with the D2E7 antibody (as described in more detail in the prior Office Action at apge 6, Tg197 mice develop disease symptoms @ 4 weeks of age while the D2E7 antibody was administered starting from teh mouse's 1st week of life), and further given the substantial differences between the etiology of rheumatoid arthritis in Tg197 mice and the etiology of rheumatoid arthritis in humans (as described in the prior Office Action at apge 8), the skilled artisan would **not** consider treating arthritis in a Tg197 transgenic mouse comprising administering 10 weekly doses of 0.1 mg/kg or 0.5 mg/kg of D2E7 starting from the mouse's first week of life to be representative of the claimed genus of treatment regimes.

As to claim 15 which recites "at a low dose of about 0.06-0.21 mg/kg at a frequency of about once per week, such that the arthritis is treated as demonstrable by mean arthritic score… and wherein arthritis is treated by alleviating at least one symptom selected from the group consisting of joint distortion, swelling of the joints, joint deformation, and ankylosis on flexion," the data of Figures 1-4, unlike that of Figure 5, would indicate to the skilled artisan that 0.1 mg/kg/week appears to be the lower limit of an effective dose in this animal model. Furthermore, given the uncertainty about how this data will translate to human treatment for the reasons of record (see the prior Office Action at pages 6-8) the skilled artisan would not recognize applicant to be in possession of the breadth of currently claimed method 15.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 stand rejected and new claims 60-62 are rejected under 35 U.S.C. § 103(a) as unpatentable over **Schattenkirchner** et al. (Presented at: The Annual Meeting of the European League Against Rheumatism (EULARO, Prague, Czech Republic, June 2001, cited herewith) in view of **den Broeder** et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42), **Salfeld** et al. (US Patent No. 6,258,562), **Kim** et al. (Arthritis & Rheumatism Vol. 43, No. 3, March 2000, pp 473–484) and **Stephens** et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010.

Applicant makes a number of arguments about the reference teachings in attempt to question the motivation to combine and reasonable expectation of success elements of the prima facie case of obviousness put forth in the prior Office Action.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010, as described below where each of applicant's arguments are addressed in turn.

As a preliminary matter, the prior rejection of record stated:

"Schattenkirchner teaches a method of treating arthritis comprising administering the human D2E7 anti-TNFα antibody at 0.5 mg/kg on a weekly basis. (see entire document, especially "Methods" and "Conclusion").

Schattenkirchner differs from the claimed invention in that it does not explicitly teach treating rheumatoid arthritis by administering 0.1 mg/kg D2E7 anti-TNFα antibody.

Den Broeder teaches a clinical study performed where three rheumatoid arthritis patients were effectively treated with the fully human D2E7 anti-TNFα antibody at a dose of 0.25 mg/kg administered either once every two weeks or once every four weeks. However, Den Broeder does not specify which treatment frequency was used for these three patients, i.e., if the patients were treated once every two weeks or once every four weeks.

Applicant's assertions on the record in their prior remarks further illustrate the teachings of Den Broeder: "as a first matter, den Broeder does not disclose the exact treatment regimens for the three patients whose dosage levels were titrated down to 0.25 mg/kg. The reference only discloses that all enrolled patients were either administered D2E7 once every two weeks or once every four weeks. **Thus, it is entirely possible that all three patients were on the once per two weeks schedule, making the lowest average dose to 0.125 mg/kg per week. Of course, in theory, it may also be possible that at least one of them was indeed on a once per 4 weeks schedule, making his / her average dose to allegedly fall within the claimed range**…" (see Remarks page 10, 1st paragraph, emphasis added).

The examiner agrees with applicant's analysis and concurs that the only certain conclusion that can be made from this particular teaching of Den Broeder is that at the very least **"all three patients were on the once per two weeks schedule, making the lowest a*verage dose to 0.125 mg/kg per week.*"**

With respect to the patients treated with 0.25 mg/kg/2-4 weeks, Den Broeder further teaches, "As no smaller dose steps than 0.25 mg/kg were included, one could speculate that even further reduction is possible for individual patients. This is supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNFα, document for…D2E7 (up to 14 weeks EULAR response)..." (see page 641, left column, 2nd paragraph).

Den Broeder further teaches that an important difference between DMARDs and anti-TNFα agents is that there is a known large variation between patients regarding the optimal dose of anti-TNFα (see Den Broeder at page 638, right col.). Den Broeder then goes on to teach that in their particular study, in spite of the relatively small number of patients, there was marked variation in the dose of D2E7 required to treat rheumatoid arthritis ranging from 4.1 to 130 mg per week, i.e., a greater than 25 fold level of variability in the dosage required for effective treatment (see Discussion page 641, left col., 2nd paragraph).

Den Broeder further teaches that by using the lowest possible dose of anti-TNFα antibody one can minimize the risk associated with TNFα suppression, such as susceptibility to some infectious disease that would normally be fought off by the proinflammatory activity of TNFα (see entire document, in particular Introduction at paragraph bridging pages 638-639 through, 1st paragraph 639, Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph). Another reason Den Broeder advocates determining the lowest effective dose of D2E7 anti-TNFα antibody is to minimize costs, which are, e.g., 200 times greater comparing the protein-based TNFα antagonist "etanercept" to the traditional DMARD methotrexate (see Den Broeder at page 639, right col., 1st paragraph).

Den Broeder ends their article with the following: "In conclusion, the dose titration of anti-TNFα treatment using the DAS28 is feasible and leads to a substantial reduction in the median dose while clinical efficacy is maintained. There is marked variation in the individual dose of anti-TNFα needed to maintain clinical efficacy. This approach will save costs and may prevent long-term side effects." (see page 641, right col.).

Moreover, Salfeld teaches a method of treating rheumatoid arthritis by administering a human anti-TNFα antibody, such as D2E7 (see entire document, in particular, e.g. column 4 last paragraph in view of column 3 first paragraph). Salfeld further teaches that an effective dose of anti-TNFα antibody is 0.1 – 20 mg/kg, and that the anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions" (see, in particular, column 25-26 bridging paragraph – col. 26 2nd paragraph).

The teachings of den Broeder regarding the reasonable possibility of yet further anti-TNFα antibody dose titration beyond 0.25 mg/kg are consistent with the teachings of Salfeld that anti-TNFα antibody dosage is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions".

Indeed, applicant's prior assertions of record at page 8, 1st paragraph of their remarks filed November 8, 2007 are further consistent with this idea: "[e]ven if, arguendo, some testing would be required to determine if the dose is affective on a particular patient, such experimentation would certainly not be 'undue' for a skilled artisan, since drug dosages have to be optimized for each patient regardless."

Therefore, it would have been obvious to one of ordinary skill in the art using the D2E7 anti-TNFα to treat rheumatoid arthritis that if they are successfully treating a patient with 0.5 mg/kg on a weekly basis consistent with the teachings of Schattenkirchner then they could and should consider further lowering the patient's dose so as to minimize cost and the risk of infectious disease induced by TNFα suppression.

Thus, it would have been obvious to one of ordinary skill in the art to titrate the dose of Schattenkirchner below 0.5 mg/kg on weekly basis.

One of ordinary skill in the art would have had a reasonable expectation of success in doing so based on the teachings of Den Broeder ("There is marked variation in the individual dose of anti-TNFα needed to maintain clinical efficacy" and "As no smaller dose steps than 0.25 mg/kg were included, one could speculate that even further reduction is possible for individual patients. This is supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNFα, document for…D2E7 (up to 14 weeks EULAR response)...") and further based on the teachings of Salfeld that an effective dose of the D2E7 anti-TNFα antibody is 0.1 – 20 mg/kg.

Additional expectation of successfully lowering the dose of Schattenkirchner comes from the teachings of Schattenkirchner itself in view of the knowledge in the art as exemplified by the teachings of Kim.

The patients being treated in the clinical study of Schattenkirchner were not treatment naïve, i.e., they were not newly diagnosed and they had previously failed a mean of 3.5 DMARDs which would imply to one of ordinary skill in the art that these patients had well-established, recalcitrant disease. Thus, effective treatment of RA in this patient population with 0.5

mg/kg D2E7 anti-TNFα antibody administration would suggest to the skilled artisan that they could reasonably expect to be able to titrate the dose of D2E7 for patients who are newly diagnosed and therefore have not already sustained irreversible joint damage (see Kim, page 473, Introduction), and therefore would be reasonably predicted to respond better to anti-TNFα treatment than the patients successfully treated by Schattenkirchner with 0.5 mg/kg/week D2E7.

Yet further expectation of successfully lowering the dose of Schattenkirchner comes from the teachings of Stephens.

Stephens teaches a clinical trial of the humanized anti-TNFα antibody CDP571 where rheumatoid arthritis were administered a single dose of 0.1, 1.0 or 10.0 mg/kg CDP571 (see page 326, 2nd paragraph).

Stephens further teaches patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see page 327, 4th paragraph).

Stephens further teaches, all patients receiving CDP571 scored a reduction in pain scale by week 1 (See page 327, 4th paragraph).

The quote from Stephens teaching the above two points is as follows: "'First infusion - Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment with maximum patient responses after 10 mg/kg....All patients who received CDP571 scored a reduction in pain scale by week 1.' See, ibid.

It is noted that applicant continues to vigorously argue the teachings of Stephens do not teach the treatment of human RA with 0.1 mg/kg humanized anti-TNFα antibody (see applicant's remarks of March 9, 2010 at pages 7-9 and the examiner's response below).

In any case, whether one of ordinary skill in the art would view the prior art teachings of Stephens as put forth above or as portrayed by applicant, the teachings of Stephens would undoubtedly be recognized by one of ordinary skill in the art to represent at least one published attempt at using a dose of 0.1 mg/kg anti-TNFα antibody, albeit an antibody far inferior to the D2E7 antibody in terms of its half-life and immunogenicity (see numerous previous Office Actions, e.g., the prior Office Action mailed December 7, 2009 at page 6), to treat rheumatoid arthritis.

In conclusion, given the teachings of Schattenkirchner to treat rheumatoid arthritis comprising administering 0.5 mg/kg D2E7 anti-TNFα as a monotherapy on a weekly basis, and further given the teachings of Den Broeder, Salfeld, Kim and Stephens that provide numerous reasons that one of ordinary skill in the art would have been motivated/had a reasonable expectation of successfully downward titrating the dosage of Schattenkirchner as outlined above, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated/had a reasonable expectation of successfully titrating the dosage of Schattenkirchner.

If dose titration of the teachings of Schattenkirchner were to lead to the claimed method of treatment then it would be the product not of innovation but of the routine optimization of a results effective variable.

In this regard it is noted that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), and see M.P.E.P. § 2144.05 II.A. Moreover, it is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272,276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804,809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious)."

Applicant's arguments

Applicant argues that because the patient population treated in den Broeder had been administered 3.0 mg/kg D2E7 for at least one year at the start of their dose titration, and were stable at this dose, and further because the patients of Schattenkirchner "applies to a more generalized patient population who had not undergone the years of treatment described in den Broeder," therefore one of ordinary skill in the art would not have been motivated to apply the teachings of den Broeder to the patients of Schattenkirchner.

This argument is not found convincing because it is unclear why one of ordinary skill in the art considering the patients of Schattenkirchner who had a substantial improvement in symptoms at 6 months that continued for the two years, i.e., these patients were being stably treated with a dose as low as 0.5 mg/kg/week, would not be motivated to titrate the dosage of antibody used to treat these patients given the teachings of Den Broeder, Salfeld, Kim and Stephens as put forth above.

Applicant further argues that "the purpose of the den Broeder study was to titrate a minimal dose suitable for individual patients. Therefore, it explicitly teaches away from a 'standard dosing schedule (used) in daily clinical practice' (page 639, top of left column), as is presently claimed." (emphasis in the original).

From this premise applicant concludes "Therefore, reading den Broeder in its proper context, one of ordinary skill in the art would not extrapolate the results described specifically in den Broeder as appropriate for individual patients to the general patient population described in Schattenkirchner who are the subject of 'standard dosing schedules in daily clinical practice,' as this goes against the very teaching of den Broeder.

For substantially the same reason, one of ordinary skill in the art also would not have had a reasonable expectation of success in modifying the standard dosing schedule in Schattenkirchner to the 'best-case-scenario' individual low dose in den Broeder calculated by the Examiner to arrive at the presently claimed invention. One of ordinary skill in the art would further have had no reasonable expectation of success in adapting a relatively low dose (that is still higher than the presently claimed dose) found to be effective in a few patients (as described in den Broeder) to a general patient population described in Schattenkirchner." (emphasis in the original).

First, it is unclear what applicant means by the presently claimed method being limited to a "standard dosing schedule (used) in daily clinical practice," perhaps it has something to do with the "frequency of about once per week" limitation??

It may be helpful to consider that den Broeder teaches "Eighteen patients flared during the study, with a mean increase in DAS28 of 1.3. Eight of these patients reported a flare between the regular 8-weekly evaluations, and the other 10 patients had their dose adjusted at the regular evaluation. Three patients did not experience a flare even on the lowest dose of 0.25 mg/kg anti-TNF-α…." (see page 640, 1st paragraph).

Considering that the dose-titration study of den Broeder went on for 48 weeks doesn't this imply dose titration is part of "daily clinical practice"?

As to applicant's conclusion that "therefore, reading den Broeder in its proper context, one of ordinary skill in the art would not extrapolate the results described specifically in den Broeder as appropriate for individual patients to the general patient population described in

Schattenkirchner…," this argument is not found convincing because, as put forth above, it is unclear why one of ordinary skill in the art considering the patients of Schattenkirchner who had a substantial improvement in symptoms at 6 months that continued for the two years, i.e., these patients were being stably treated with a dose as low as 0.5 mg/kg/week, would not be motivated to titrate the dosage of antibody used to treat these patients given the teachings of Den Broeder, Salfeld, Kim and Stephens as put forth above.

Applicant's argument does not convincingly rebut why one of ordinary skill in the art would not have been motivated and had a reasonable expectation of successfully downward titrating the adalimumab dose of any given RA patient stably responding to 0.5 mg/kg/week (per Schattenkircher) or a dose of 0.25 mg/kg/2 weeks (per den Broeder) in view of the reference teachings.

Applicant argues they dispute that Salfeld teaches dose range and administration frequency are results effective variables for the reasons of record. The examiner disagrees for the reasons of record put forth above.

Applicant argues the instant claims do not require that the patient being treated is newly diagnosed, and therefore any argument related to the reasonable expectation of success one of ordinary skill in the art would have about using low dose adalimumab to treat RA in a newly diagnosed patient is not valid for that reason.

The examiner agrees with applicant that the claims are not limited to the treatment of newly diagnosed patients; however, the instant claims do encompass the treatment of newly diagnosed patients in their breadth and for that reason applicant's argument is not found convincing.

Applicant makes a number of arguments about the teachings of Stephens. Much of this has been extensively covered in previous Office Actions as shown above.

The key position of the examiner is that however one of ordinary skill in the art would interpret the teachings of Stephens, these teachings would undoubtedly be recognized by one of ordinary skill in the art to represent at least one published attempt at using a dose of 0.1 mg/kg anti-TNFα antibody, albeit an antibody far inferior to the D2E7 antibody in terms of its half-life and immunogenicity (see numerous previous Office Actions, e.g., the prior Office Action mailed December 7, 2009 at page 6), to treat rheumatoid arthritis.

That said, the examiner would like to point out a few things about applicant's interpretation of the teachings of Stephens.

Applicant argues "In fact, even assuming for the sake of argument that this 'all patients' sentence above does pertain to the 0.1 mg/kg treatment group (which Applicants do dispute, see argument in the previous response), this is the only literal teaching in Stephens that explicitly pertains to the efficacy of the 0.1 mg/kg treatment group. Aside from having shown

no actual data for the extent of the reduction, any alleged efficacy of the 0.1 mg/kg treatment group is severely undermined by the data in Table 2 showing that the placebo group also had a sizeable pain score reduction after week 1. Applicants note that the Examiner does not disagree with this argument."

It is the examiner's position that it is unclear what "the data in Table 2 showing that the placebo group also had a sizeable pain score reduction after week 1" would imply to one of ordinary skill in the art about the efficacy of administering 0.1 mg/kg anti-TNFα antibody.

First, it is unclear why applicant thinks this is a "sizeable pain score reduction" compared to the patients receiving 1 or 10 mg/kg treatment shown in Table 2. Secondly, given that the pain score goes up and down seemingly at random looking across all weeks for the placebo treated patients strongly suggests this measure is subject to great variability. Lastly, even setting aside these first and second issues, one of ordinary skill in the art would expect to see a placebo on pain a week after the first dose of placebo.

As to applicant's argument (referring to Stephens) that "…the lack of any conclusive data for the 0.1 mg/kg data, in combination with the marginally effective effect from the 1 mg/kg treatment group, would likely discourage one of skill in the art not to lower the 0.5 mg/kg Schattenkirchner dose any further, let alone 2- to 5-fold further," the examiner disagrees with the characterization of 1 mg/kg as "marginally effective" given the results reported on pages 229-30 of Stephens; moreover, applicant's argument is also not convincing because it does not take into account that one of ordinary skill in the art would understand the Stephens antibody to be far inferior to the D2E7 antibody in terms of half-life and immunogenicity as discussed by both applicant and the examiner in many prior Office Actions, see, e.g., the prior Office Action mailed December 7, 2009 at page 6.

6. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 stand rejected and new claims 60-62 are rejected under 35 U.S.C. § 103(a) as unpatentable over **den Broeder** et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) in view of **Salfeld** et al. (US Patent No. 6,258,562), essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010.

   Applicant argues the instant rejection should be withdrawn for the some of the same reasons as the rejection discussed in the preceding section.

   Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010, as described in the preceding section.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

MPEP § 2173.05 states:

"When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree. If it does not, a determination is made as to whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. Even if the specification uses the same term of degree as in the claim, a rejection may be proper if the scope of the term is not understood when read in light of the specification. While, as a general proposition, broadening modifiers are standard tools in claim drafting in order to avoid reliance on the doctrine of equivalents in infringement actions, when the scope of the claim is unclear a rejection under 35 U.S.C. 112 <http://www.uspto.gov/web/offices/pac/mpep/documents/appxl_35_U_S_C_112.htm>, second paragraph, is proper. See In re Wiggins, 488 F. 2d 538, 541, 179 USPQ 421, 423 (CCPA 1973).

When relative terms are used in claims wherein the improvement over the prior art rests entirely upon size or weight of an element in a combination of elements, the adequacy of the disclosure of a standard is of greater criticality.

**>In determining the range encompassed by the term "about", one must consider the context of the term as it is used in the specification and claims of the application. Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd., 476 F.3d 1321, 1326, 81 USPQ2d 1427, 1432 (Fed. Cir. 2007). In< W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite because infringement could clearly be assessed through the use of a stopwatch. However, the court held that claims reciting "at least about" were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about." Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)."

The instant claims recite "at a low dose of about 0.06-0.21 mg/kg" (see claims 15, 21, 42, 48) and similar like claim 62 "wherein the low dose is about 0.09-0.11 mg/kg." The metes and bounds of this limitation would not be clear to the skilled artisan because the instant specification does not provide any explicit guidance or direction as to what is meant by the relative term "about" as it is applied to the mg/kg antibody being administered in the instant claims.

For example, the spec discloses dose of "about 0.01 - 2.0 mg/kg" or "about 0.06 - 1.9 mg/kg" or "about 0.11 - 1.8 mg/kg" etc. following the pattern add 0.05 mg/kg to lower limit and

subtract 0.1 mg/kg from upper limit, and further stating that any range intermediate to the above dosages is included, e.g. about 0.17 – 1.65 mg/kg. So what does this mean about "about," i.e., how can the skilled artisan be expected to draw a generalization about what is meant by "about" from the regular repeating pattern above when any range intermediate to the above dosages is also included?

9. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (20010021380, cited on an IDS).

Pluenneke teaches a method of treating RA comprising administering the D2E7 anti-TNFα antibody at a dose of 0.1 – 20 mg/kg on a weekly basis (see paragraphs 29, 32 and 67).

Given that the range of Pluenneke 0.1 – 20 mg/kg overlaps the claimed range – "about" 0.06 - 0.21 mg/kg – and further given the uncertainty about the meaning of "about" put forth above, it is prima facie obvious that one of ordinary skill in the art following the teachings of Pluenneke would arrive at the claimed method of treatment.

This because, as is made clear from the teachings of Pluenneke, e.g., at paragraphs 22-29, the determination of the dosage regimen of a known drug is well within the purview of one of ordinary skill in the art at the time the invention was made, and it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal intervals of treatment because optimal intervals is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. Although the prior art does not explicitly teach the dosage regimen as claimed, it would be conventional and within the skill of the art to identify the optional dosages administered. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. It is clear that both the prior art and claimed method administer the same antibody to achieve the same results. It would be conventional and within the skill of the art to determine the optimal dosage regimens. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP §§ 2144.05 part II A.

Lastly it should be noted that in the case where claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990), see MPEP § 2144.05.

10. No claims are allowed.

11. Applicant's claim amendments and submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 11-16-2010 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS**

MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Phuong N. Huynh can be reached on 571-272-0846. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Primary Examiner, Art Unit 1644